REMARKS

Reconsideration of this application, as amended, is respectfully requested.

Claims 24, 27-30, 31-39, 49-53, 67-68 and 69-106 were pending at the issuance of the instant Office Action. Claims 24, 27-39, 77, 79, 81, 86-94, 97-101 and 104-106 have been cancelled without prejudice or disclaimer. Claims 69, 78, 80, 82, 83, 95, 96, and 103 have been amended to more clearly reflect the invention or correct typographical errors. Also, new pages 82-117, representing the Sequence Listing, have been inserted. Support for these amendments can be found within the specification as originally filed. New claims 107-115 have been added. Applicants maintain that no new matter has been added as a result of the above-described amendments. Claims 49-53, 67-76, 78, 80, 82-85, 87-105, and 107-115 are now pending. A clean copy of the claims, as amended, is attached as **Exhibit A**.

Turning to the Office Action, claims 24, 49-53, 67-68, 69-106 stand rejected under 35 U.S.C. § 112, first paragraph for a lack of enablement. Claims 24, 49-53, 67-68, and 69-106 stand rejected under 35 U.S.C. § 102(e) as being anticipated by, or in the alternative obvious under 35 U.S.C. § 103(a) over Wallach et al. ("Wallach"; U.S. Patent No. 5,695,953). Applicants respectfully traverse these rejections.

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

Claims 24, 49-53, 67-68, 69-106 stand rejected under 35 U.S.C. § 112, first paragraph for a lack of enablement of N and/or C-terminal amino acid deletions. During the February 2, 1999 in-person interview with John McDonnell, the Examiner indicated that the enablement rejections related to the N-terminal and C-terminal additions or deletions would be withdrawn. Applicants submit that the pending claims are fully supported by the specification. Accordingly, Applicants respectfully request that the rejections of claims 24, 49-53, 67-68, and 69-106 under 35 U.S.C. § 112, first paragraph be withdrawn.

It should be noted that claim 24 has been cancelled and is not further discussed.

REJECTION UNDER 35 U.S.C. § 102(e) OR, ALTERNATIVELY, 35 U.S.C. § 103(a)

Claims 49-53, 67-68, and 69-106 stand rejected under 35 U.S.C. § 102(e) as being anticipated by, or in the alternative obvious under 35 U.S.C. § 103(a) over Wallach et al. ("Wallach"; U.S. Patent No. 5,695,953). Applicants respectfully disagree as indicated below.

SUMMARY ARGUMENT

Applicants maintain that Wallach is not a reference that may serve as the proper basis for rejection of the instant claims under either 35 U.S.C. § 102(e) or 103(a). As described below, Applicants maintain that Wallach provides only a partial and incomplete amino acid sequence of the TNF inhibiting protein (TNF-IP) and is completely silent as to DNA sequences encoding such protein. Consequently, Wallach does not provide a written description of the invention. As evidence, it is shown through declaration and Wallach's own published literature that Wallach himself, in his own after filing publications could not follow the procedures of the '953 specification in a straightforward manner to isolate either the complete amino acid sequence of TNF-IP or a DNA encoding TNF-IP. In addition, the repeated attempts by others skilled in the art to isolate such a DNA molecule using the methods provided by the Wallach specification failed. And, finally, the disclosure provided by Wallach fails to meet the written description and enablement requirements put forth by the Federal Circuit prior to and following allowance of the Wallach claims.

A. REJECTION UNDER 35 U.S.C. § 102(e)

To serve as a proper reference to support a 35 U.S.C. 102 rejection, the reference must disclose every aspect of the invention against which it is applied. As a general rule, for prior art to anticipate under § 102, every element of the claimed invention must be identically disclosed in a single reference. *Corning Glass Works v. Sumimoto Electric*, 9 U.S.P.Q.2d 1962, 1965 (Fed. Cir. 1989). The exclusion of a claimed element, no matter how insubstantial or obvious, from a reference is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. 1093, 1098 (Fed. Cir. 1983). Applicants maintain

herein that Wallach does not disclose Applicants' invention and, therefore, cannot form the basis of a proper 35 U.S.C. § 102 rejection of the claims.

Wallach relates to the isolation and partial purification of a "TNF inhibitory protein." Completely absent from Wallach is any DNA sequence information related to a DNA molecule encoding the TNF inhibitory protein. Only minimal and incomplete amino acid sequence is provided at column 4, middle section; column 10, middle section; and, column 12, middle section. The amino acid sequence thus provided is "Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser" where X is unknown and Cys at the fourth position is theoretical (col. 4, lines 24-36). While certain portions of this partial and incomplete amino acid sequence shares some identity with the instantly claimed polypeptides, Wallach provides no information as to the remaining amino acid sequence of the TNF inhibitory protein or any DNA sequence that may encode such a protein. At best, Wallach has only disclosed a partial and incomplete amino acid sequence and a general description of a method that may be used to determine the full amino acid sequence and isolate a DNA sequence encoding the polypeptide. Thus, Wallach has not disclosed each and every element (i.e., the complete amino acid sequence or the DNA sequence) of the instantly claimed invention. Applicants maintain that rejection of claims 49-53, 67-68, and 69-106 as being anticipated by Wallach under 35 U.S.C. § 102(e) is improper. Accordingly, Applicants respectfully request that the rejections be withdrawn.

B. REJECTIONS UNDER 35 U.S.C. § 103(a)

1. *Graham v. John Deere*

In making a determination of obviousness, the U.S. Supreme Court has determined the factual inquiries upon which the decision-maker should premise the ultimate conclusion. See *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966). These inquiries are:

a. the scope and content of the prior art;

b. the differences between the prior art and the claims at issue;

c. the level of ordinary skill in the art; and,

d. objective indicia of nonobviousness, if any.

The Court in *Graham* further identified the objective indicia to include, for example, commercial success, long-felt but unsolved need, and failure of others as factors to be considered in making an obviousness determination. *Id.*

The present invention discloses the complete amino acid nucleotide sequence of a TNF binding protein ("TNF-BP"). Wallach provides only the partial and incomplete amino acid sequence of a TNF inhibitory protein ("TNF-IP") and does not disclose any nucleotide sequence whatsoever. As described below, consideration of each of these factors in turn and in combination leads to the only possible conclusion: the claimed invention cannot be found to be obvious in view of Wallach. It will be shown that: 1) Wallach does not disclose a complete amino acid sequence of TNF-IP; 2) Wallach does not disclose any DNA sequence; and 3) the paper examples[1] provided by Wallach were not sufficient to enable the skilled artisan or even Wallach himself to isolate either the complete amino acids sequence or a DNA sequence encoding TNF-IP (termed "TNF-BP" by the instant applicants). In contrast, the instant applicants have provided both a full-length amino acid sequence and a complete DNA sequence encoding the TNF-BP. Applicants believe that consideration of the *Graham* factors leads to the ultimate conclusion that Wallach does not render the instantly claimed invention obvious.

a. The first *Graham v. John Deere* factor: the scope and content of U.S. Patent No. 5,695,953 (hereinafter "Wallach")

A proper obviousness rejection can be supported by an explicit or implicit disclosure by a prior art reference that discloses the claimed invention. It is also required that the disclosure must be enabling. Wallach does not provide either an explicit or an implicit disclosure of the instantly claimed invention. In addition, as attested to by Dr. John Mountz in his declaration (attached as **Exhibit C**), Wallach does not enable the instantly claimed invention.

[1] At col. 10, line 57, Wallach begins a discussion of speculative examples related to "Genetic Engineering of the TNF Inhibitory Protein." It is apparent from publications subsequent to the filing of the application that the methods provided by the application could not be utilized to either determine the complete polypeptide sequence or isolate a DNA sequence encoding the protein.

(1.) The Wallach specification does not explicitly describe either the complete amino acid sequence of sTNF-IP or a DNA molecule encoding TNF-IP.

Wallach describes the sTNF-IP protein as a:

> ...substantially purified protein, which is free of proteinaceous impurities, [and] has a molecular weight of 26-28 kDa when analyzed on SDS-PAGE under reducing conditions... (col 4, lines 14-16)

The sole disclosure of a sequence of any kind is the partial and incomplete amino acid sequence provided at column 4, middle section; column 10, middle section; and, column 12, middle section. The amino acid sequence and description thereof provided is:

> ...Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser wherein the amino acid designated X at the 14th position *was not identified* and the presence of cysteine (Cys) at the 4th position is *theoretical*... (Emphasis added.)

It is suggested that this amino acid sequence represents the N-terminus of the TNF inhibitory protein. Wallach provides no additional information as to the remaining amino acid sequence of the sTNF-IP. Wallach does not provide any DNA sequence whatsoever. At least a portion of the amino acid is, in the words of Wallach, "not identified" and "theoretical." Thus, the amino acid sequence provided by Wallach is *both partial and incomplete*.

Consistent with recent holdings by the Federal Circuit, Wallach has not described the sequence of the instantly claimed invention. The Federal Circuit held that, for a DNA molecule to be described, the sequence of the DNA molecule must be set forth. As held in *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (and later cited by *Regents*, below):

> [A]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and a reference to a potential method for isolating it; *what is required is a description of the DNA itself.* (Emphasis added) *Fiers* at 1170.

As described above, Wallach has not provided a description of the instantly claimed invention. Wallach provides neither a disclosure of a complete amino acid sequence of a TNF inhibiting protein or a DNA sequence encoding such a protein. Accordingly,

Applicants do not believe Wallach is a proper reference to support a 35 U.S.C. § 103 rejection of the instant claims.

(2.) The Wallach specification does not implicitly describe either the complete amino acid sequence of sTNF-IP or a DNA molecule encoding TNF-IP.

The disclosure by Wallach of a partial and incomplete amino acid sequence does not implicitly render either the complete amino acid sequence or the DNA sequence encoding such an amino acid sequence obvious. Wallach provides only a hypothetical plan for isolating the complete amino acid sequence and/or DNA sequence encoding the instantly claimed TNF-inhibitory protein. And, as described by Dr. Mountz in his declaration (**Exhibit C**; "Mountz"), the speculative plan provided by Wallach did not provide the skilled artisan with the required tools to derive the instantly claimed invention as of the filing date. As held by the Federal Circuit, a plan or wish for obtaining a claimed chemical invention is not a description of such an invention. *Regents of the State of California v. Eli Lilly & Co.*, 119 F.3d. 1559 (Fed. Cir. 1997). In *Regents*, the Court held that such an invention "requires a precise definition, such as by *structure, formula, chemical name, or physical properties*." *Regents* at 1566.

In addition, the disclosure of the amino acid sequence of a protein does not render obvious a claim to a specific nucleic acid sequence. *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993). That Court stated:

> ...because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein...given the nearly infinite number of possibilities suggested by the prior art, and the failure of the prior art to suggest which of those possibilities is the human sequence, the claimed sequence would not have been obvious. *Bell* at 784.

Similarly, in *In re Deuel*, it was held that the:

> "...redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein." *In re Deuel*, 51 F.3d 1555, 1558 (Fed. Cir. 1995).

The partial and incomplete amino acid sequence provided by Wallach does not render the instantly claimed invention obvious. One could not predict from that partial and incomplete amino acid sequence either the complete amino acid sequence of TNF-IP

E

or the DNA sequence encoding TNF-IP. Thus, the disclosure of Wallach, providing only a partial and incomplete amino acid sequence of a TNF-inhibitory protein, does not implicitly disclose either the complete amino acid sequence of the protein or a DNA molecule encoding the protein. Consistent with recent Federal Circuit holdings, the disclosure of only a partial and incomplete amino acid sequence cannot be said to implicitly disclose the instantly claimed invention.

(3.) Wallach does not enable the instantly claimed invention.

In view of 1 and 2 above, the only way a rejection of the instant claims over Wallach could potentially be proper would be if the disclosure was sufficient to place the instantly claimed invention into the hands of the skilled artisan. As described above, Wallach relates to the partial isolation and purification of a "TNF inhibitory protein." Wallach provides only a partial and incomplete amino acid sequence as follows: Asp-Ser-Val-Cys-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-X-Asn-Ser "wherein the amino acid designed X at the 14th position was not identified" and the "Cys" residue at position 4 of the sequence as "theoretical" (see col. 4, line 32-34).

As attested to by Dr. John Mountz in the attached declaration (hereinafter "Mountz"; **Exhibit C**), the Wallach patent taught three hypothetical methods for isolating a TNF Inhibitory Protein (TNF IP) cDNA. As described therein, none of these approaches had been carried out as of the filing date of Wallach (Mountz, para. 10-24). In addition, Dr. Mountz describes multiple, repeated failures by both Wallach and other skilled artisans to isolate the complete amino acid sequence of TNF-IP and a recombinant DNA encoding the same.

Three speculative methods for isolating a DNA encoding TNF-IP were described by the '953 patent (Mountz, para. 16, 17, and 20). The first two of the speculative methods were dependent upon identifying a cultured cell line expressing TNF-IP and preparing a cDNA library from that cell line (Mountz, para. 13). The '953 patent suggested that such a cell line could be found through immunofluorescence or Western blotting using an antibody directed against TNF-IP (Mountz, para. 13). Such an antibody was to be obtained by injecting rabbits or mice with either purified TNF-IP or a synthetic peptide corresponding to the "known" amino acid sequence of an N-terminal fragment of

TNF-IP (Mountz, para. 14). Alternatively, Wallach taught that such an antibody could be derived by preparing a fusion construct using the putative N-terminal amino acid sequence of the TNF-IP fragment and expressing this construct in E. coli (Mountz, para. 14). Once a cell line expressing TNF-IP was identified, poly A^+ mRNA would be isolated, and converted to cDNA using an oligo-dT primer and reverse transcriptase (Mountz, para. 15).

In the first approach for cloning TNF-IP, Wallach suggested that the cDNA obtained from TNF-IP expressing cells would be cloned into an expression vector such as λgt11 and a TNF-IP cDNA identified by screening such a cDNA library with the anti-TNF-IP antibody (Mountz, para. 16). The second approach taught by Wallach would utilize a mixture of degenerate oligonucleotides produced from the predicted nucleotide sequence of the N-terminal peptide of the putative disclosed TNF-IP protein to screen a cDNA library using methods known in the art (Mountz, para. 17). Wallach also taught that additional peptide sequences could be obtained from proteolytic fragments of TNF-IP (Mountz, para. 18). Degenerate oligonucelotides could be designed based on the TNF-IP amino acid sequence following "codon usage rules" as set forth by Lathe et al. (*J. Molec. Biol.* 183: 1 (1985)), so the mixture would be likely to contain an oligonucleotide having a sequence approximately matching the TNF-IP cDNA (Mountz, para. 19).

The last of the three approaches suggested by Wallach for isolating a DNA molecule encoding TNF-IP involved screening a human genomic library with a degenerate oligonucleotide probe as described for the cDNA libraries (Mountz, para. 20).

Dr. Mountz avers that there was no disclosure of any of the cloning experiments described in the '953 patent, and no evidence that any of the experiments had actually been carried out as of the filing date of the '953 patent (Mountz, para. 21-24). As attested to by Dr. Mountz, Wallach did not disclose: 1) the nucleotide sequence nor production of any oligonucleotide, degenerate oligonucleotide, of mixture of oligonucleotides (Mountz, para. 22); 2) the identity of a cell line expressing TNF-IP (Mountz, para. 23); or, 3) the screening of a cDNA or genomic DNA library or a DNA molecule encoding TNF-IP (Mountz, para. 24).

Dr. Mountz also describes a series of patent publications and other publicly available references where some or all of the inventors named in the '953 patent reported

several unsuccessful attempts to isolate a TNF-IP DNA molecule according to the methods of the '953 patent (Mountz, para. 26-33). For example, Dr. Mountz describes Israeli patent application IL 92697 which discloses Wallach's failure to obtain a TNF-IP cDNA by screening oligo-dT primed cDNA libraries derivded from human liver, human placenta, HeLa, or U937 cell lines using a mixture of degenerate oligonucleotides corresponding to nucleotide sequences predicted to encode the N-terminal amino acid sequence of TNF-IP (Mountz, para. 29). This result was obtained in spite of the fact that: 1) U937 was later shown to express TNF-IP mRNA (Mountz, para. 29).

The same researchers obtained a positively-hybridizing cDNA fragment, designated "C2", from a randomly-primed colon cDNA library using a degenerate probe containing the nucleotide base inosine which was not described by the '953 patent (Mountz, para. 30-33). C2 includes a number of bases that differ from the instantly claimed sequences (Mountz, para. 31). C2 was then unsuccessfully utilized as a secondary probe (not described by the '953 patent) to re-screen the colon cDNA library and an oligo-dT primted placental cDNA library (Mountz, para. 32-33).

It was not until the publication by Nophar et al. (after the filing date of the '953 patent) that the inventors provided evidence a TNF-IP cDNA clone had been isolated (Mountz, para. 34-39). Nophar screened a commercially available randomly-primed λZAP cDNA library derived from CEM lymphocytes (unavailable as of the '953 filing date) using the C2 probe (Mountz, para. 35, 36). The reason CEM was chosen is not apparent but these were not identified as TNF-IP expressors as suggested by the '953 patent (Mountz, para. 37). Nophar demonstrates that the '953 patent did not enable either the inventors themselves or another ordinary skill artisan to produce a recombinant DNA encoding TNF-IP (Mountz, para. 38, 39).

The difficulty in isolating TNF-IP cDNA by screening a cDNA library using a degenerate oligonucleotide mixture is further highlighted by the unsuccessful attempts of other skilled artisans at sophisticated, well-funded and motivated companies like Genentech, Boehringer Ingelheim, and Hoffman La-Roche (Mountz, para. 40-72). For instance, according to Dr. Mountz each of the research groups was required to creatively resolve critical issues left unresolved by the teachings of the '953 patent (Mountz, para. 41).

As attested to by Dr. Mountz, researchers at Hoffman La-Roche failed to isolate a TNF-IP cDNA using "conventional cloning" techniques which proved to be "technically difficult" (Loetscher et al., 1990, *Cell* 61:351-59; Mountz, para. 42-48). The cDNA libraries unsuccessfully screened using conventional methods included those generated from human placental or HL60 mRNA (Mountz, para. 43). Neither human placental tissue nor HL60 were identified by the '953 patent to be TNF-IP expressors (Mountz, para. 46, 47). Ultimately, polymerase chain reaction (PCR) (not disclosed by the '953 patent) was utilized to generate a 78 bp probe used to isolate a TNF-receptor encoding cDNA from a human placental λgt11 cDNA library (Mountz, para. 44, 48). One of the PCR primers utilized was complementary to an internally derived amino acid sequence; the '953 patent does not disclose any such fragment (Mountz, para. 45). Thus, the Hoffman-LaRoche researchers were not successful in isolating a TNF-IP encoding cDNA using the techniques discussed in the '953 patent. There was no disclosure in the '953 patent of either a DNA probe produced by PCR or a human placenta cDNA library (Mountz, para. 48).

As another example, Dr. Mountz describes the unsuccessful attempts by researchers at Boehringer Ingelheim to utilize the methods of the '953 patent to isolate a TNF-IP encoding cDNA (Mountz, para. 49-55). As detailed in EP 417563, these researchers unsuccessfully screened oligo-dT primed U937, Hs913T, or HeLa cDNA libraries using mixtures of degenerate oligonucleotide probes generated from the N-terminal amino acid sequence of the '953 patent (Mountz, para. 49, 50). The Boehringer Ingelheim researchers then generated a PCR fragment (not disclosed by the '953 patent) corresponding to the sequence of an internal tryptic peptide fragment (not disclosed by the '953 patent) (Mountz, para. 51, 52). EP 417563 does not indicate that Hs913T cells are TNF-IP expressors (Mountz, para. 53, 54). Thus, the Boehringer Ingleheim researchers were not able to utilize the teachings of the '953 patent to isolate a cDNA encoding TNF-IP (Mountz, para. 55).

As described by Dr. Mountz, researchers at Genentech reported the cloning of the TNF receptor by screening λgt10 placental and HL60 cDNA libraries following using non-degenerate oligonucleotides designed based on internal amino acid sequence of the receptor (Schall et al., 1990, *Cell* 61: 361-70; Mountz, para. 56-63). Internal proteolytic

fragments of the TNF receptor protein (not described by the '953 patent) were produced and a non-degenerate oligonucleotide probe (not described by the '953 patent) was designed based on the sequences obtained therefrom (Mountz, para. 57-60). The Genentech researchers obtained four hybridizing clones from a randomly-primed library and a single positively-hybridizing clone from an oligo dT-primed library (Mountz, para. 58). Thus, Dr. Mountz avers, the Genentech researches were only able to isolate a hybridizing cDNA from a cDNA library produced in placenta or HL60 (not identified by the '953 patent as TNF-IP expressors) and an internally-derived oligonucleotide (not disclosed by the '953 patent) (Mountz, para. 63).

In yet another example, Dr. Mountz describes the cloning of a TNF receptor cDNA by researchers at Synergen (Mountz, para. 64-72). Initially, these researchers utilized an N-terminal degenerate probe to isolate a clone encoding 68 amino acids (Mountz, para. 66). A probe corresponding to the internal sequence was then utilized to screen an oligo-dT-primed cDNA library of U937 cells, from which three clones were identified, which were confirmed using a second probe derived from internal amino acid sequence (Mountz, para. 67, 68). Internal amino acid sequences were not disclosed by the '953 patent (Mountz, para. 68). The researchers did not identify U937 as being TNF-IP expressors using immunofluorescence or western blotting (Mountz, para. 69, 70). In fact, Engelmann et al. (*J. Biol. Chem.* 264: 11974-19980) produced monoclonal antibodies generated against affinity purified TNF-IP (Mountz, para. 71). Thus, the Synergen researchers were successful in obtaining a cDNA clone only when they used a cDNA library from the HL60 cell line (not first identified as a TNF-IP expressor) and a sequence encoding an internal peptide sequence (Mountz, para. 72).

It is Dr. Mountz' expert opinion that the '953 patent would not have enabled one of ordinary skill in the art to obtain a DNA molecule encoding TNF (Mountz, para. 73-83) and provides the details of his reasoning in para. 75-82) of his declaration. The reasons outlined therein include: 1) the fact that TNF-IP is a proteolytic cleavage fragment of the TNF receptor was not known as of the filing date of the '953 patent (Mountz, para. 75); 2) the protein preparation prepared using the biochemical separation protocol of the '953 patent is very impure and this would make it difficult to prepare and screen antibodies (Mountz, para. 76); 3) the level of impurity would have led the

ordinary skilled artisan to believe that the peptide sequence of the '953 patent could not be relied upon (Mountz, para. 78); 4) until a cDNA clone was isolated, it could not have been established that the protein having the disclosed N-terminal amino acid sequence bound to TNF (Mountz, para. 79); 5) no cDNA libraries or porbes were disclosed by the '953 patent (Mountz, para. 80); 6) the '953 patent provides only limited sequence information and an encyclopedia of experimental options (Mountz, para. 81); and, 7) the disclosed amino acid sequence and the absence of an identified cell source would have provided insufficient information to clone the DNA (Mountz, para. 82).

Thus, Dr. Mountz concludes, the '953 patent would not have enabled one of ordinary skill in the art to obtain a DNA molecule encoding TNF-IP using the methods set forth therein.

(4.) Wallach does not explicitly or implicitly disclose nor enable the instantly claimed invention.

As described above, Wallach neither explicitly nor implicitly discloses the complete amino acid sequence of TNF-IP or a DNA sequence encoding the protein. And, as attested to by Dr. Mountz, the '953 patent does not enable the skilled artisan to either determine the complete amino acid sequence or a DNA molecule encoding TNF-IP. As described by Dr. Mountz, both the inventors of the '953 patent and several other highly skilled groups of investigators were unsuccessful in utilizing the methods described in the '953 patent to completely characterize the TNF-IP protein or a DNA encoding the same. The Federal Circuit has held that failure of others is almost irrefutable evidence of non-obviousness (Markey, C.J., *Panduit v. Dennison Manufacturing*, 774 F.2d 1082 (Fed.Cir. 1986)).

In fact, during prosecution of a European patent application directed to similar material, Wallach's counsel stated on page 3 of a communication to the EPO:

> The "gap" between [the reference] and the claimed subject matter can be seen by the provision of the tools and means for expression of TBP-I in a recombinant fashion in the host cell. To fill this gap, it certainly requires an inventive step...isolation of cDNA clones with this probe, characterisation of the isolated clones, and determination of the

F

nucleotide sequence of the insert C2...fills in the gap... (**Appendix M** of the Mountz Declaration).

Thus, the inventors themselves considered the determination of the nucleotide sequence to be a significant finding.

The '953 patent does not explicitly or implicitly describe the instantly claimed invention, and does not enable the skilled artisan to obtain the claimed invention. As such, the instant claims cannot be held to be obvious under 35 U.S.C. § 103(a). Accordingly, Applicants respectfully request that these rejections be withdrawn.

b. The second *Graham v. John Deere* factor: differences between the prior art and the instant invention

The instant invention relates to TNF-binding polypeptides (hereinafter "TNF-BP") encoded by specifically defined recombinant DNA molecules. Wallach provides only partial and incomplete amino acid sequence for the TNF-IP disclosed in the '953 patent and does not describe *any* recombinant DNA molecules. The differences between the Wallach and the instant invention are substantial. Applicants teach the claimed invention; Wallach does not.

The instant claims are directed to polypeptides and specific variations thereof which are specifically described by the instant specification. For the Examiner's convenience, Applicants provide a complete copy of the pending claims, as amended herein, as **Exhibit A**. Also for the Examiner's convenience, Applicants attach herewith as **Exhibit D** a color coded scheme corresponding to the various portions of the sequences claimed in the claims 78, 80, and 103 (as an example).

Claims 49-53, 69-76, 78, 80, and 82 are directed to a polypeptide or a C-terminally or N-terminally shortened version thereof encoded by a specific DNA sequence or fragment which is described at, for example, page 3, line 34 to page 4, line 31 and Figure 1 of the instant specification. In addition, the polypeptide is either non-glycosylated or has a glycosylation pattern provided following expression in Chinese Hamster Ovary (CHO) cells.

For example, the sequences in part A of claim 69 is illustrated at page 4, lines 37-48. The sequence of part B of claim 69 is contained within the sequence described at

page 4, lines 1-14. The sequence of part B merely extends the sequence of part A by 10 codons (GTT AAG GGC ACT GAG GAC TCA GGC ACC ACA; 30 nucleotides corresponding to an additional 10 amino acid residues) that are described at page 4, lines 14-15. These sequences are also illustrated within Figure 1; sequence A corresponds to nucleotide 333 to 815 (amino acid residues 12 to 172) and sequence B to nucleotides 333 to 845 (amino acid residues 12 to 182).

As another example, the DNA sequences encoding the polypeptides of claim 78 are also contained within the specification at page 3, line 34 to page 4, line 31 and Figure 1. The polypeptides of claim 78 are encoded by the DNA sequence found within the specification as follows: 1) part A: beginning at the CTG codon on line 1 of page 4 and ending with the AAT codon at line 13 of page 4; 2) part B: beginning with the CTG codon at line 1 of page 4 and ending with the ACA codon at line 14, line 4; 3) part C: beginning with the GAT codon at line 1 of page 4 to the AAT codon at line 13 of page 4; and, 4) part D: beginning with the GAT codon of line 1 of page 4 to the ACA codon at line 14, line 4.

As yet another example, the DNA sequences of claim 80 are described at page 3, line 34 to page 4, line 31 and Figure 1 of the instant specification. The polypeptides of claim 80 are encoded by the DNA sequence found within the specification as follows: 1) part A: a single ATG codon adjacent to the CTG codon on line 1 of page 4 and ending with the AAT codon at line 13 of page 4; 2) part B: a single ATG codon adjacent to the CTG codon at line 1 of page 4 and ending with the ACA codon at line 14, line 4; 3) part C: a single ATG codon adjacent to the GAT codon at line 1 of page 4 to the AAT codon at line 13 of page 4; 4) part D: a single ATG codon adjacent to the GAT codon of line 1 of page 4 to the ACA codon at page 4, line 14; 5) part E: the segment from the ATG codon on page 3, line 34 to the AAT codon at page 4, line 13; 6) part F: the segment from the ATG codon at page 3, line 34 to the ACA codon at page 4, line 14; 7) part G: the segment beginning with the ATG codon at page 3, line 34 and ending with the GGA codon at page 4, line 1 adjacent to the segment beginning with the GAT codon at page 4, line 1 to the AAT codon at page 4, line 13; 8) part H: the segment beginning with the ATG codon at page 3, line 34 and ending with the GGA codon at page 4, line 1 adjacent to the segment beginning with the GAT codon at page 4, line 1 to the ACA codon at page

F

4, line 14; and, 9) part I: the segment beginning with the ATG codon at page 3, line 34 to the TGA codon at page 4, line 31.

Claims 70-76 are directly or indirectly dependent on claim 69 and relate to modifications of the claimed polypeptide that are within the capabilities of the ordinary skilled artisan. "R^2" is defined at page 5, lines 1-2 as representing a "...DNA coding for a polypeptide which can be cleaved in vivo...," as claimed in claim 70. Claims 71 and 72 are directed to a polypeptide of claim 69 where R^2 is a DNA molecule comprising amino acid sequence found N-terminal to the sequence of claim 69. The sequence described in claims 71 and 72 can be found within the specification at page 4, line 1 and Figure 1. Claims 73 and 74 refer to an "R^3" sequence defined therein as a "DNA coding for a signal peptide." Sequences encoding signal peptides are well-known and widely available in the art and could be easily obtained and utilized by one skilled in the art. For example, the R^3 sequence of claim 75 is specifically described at page 3, line 34 to page 4, line 1 and encodes the polypeptide sequence of claim 76.

Claim 82 is also dependent upon claim 69, and is directed to a polypeptide encoded by a "...nucleic acid which hybridizes with DNA complementary to the DNA...under conditions of moderate stringency." Applicants maintain that "conditions of moderate stringency" are described, for example, at page 62, lines 18-24 of the instant specification (i.e., hybridization in 6X SSC/ 5X Denhardt's/ 0.1% SDS).

Claims 83 and 103 are directed to polypeptides for which the sequences are described on page 5, line 16 to page 6, line 4 of the instant specification. Claims 49-53, 84, 85, 87-102, and 109 are dependent on claim 83 and include modifications of the polypeptides of claim 33 that are within the skills of the ordinary artisan. For example, such modifications include C- and/or N-terminally shortened sequences (claim 85), intrasequence conservative substitution (claim 87), substitution at a glycosylation site (claim 93, 94). These types of substitutions are fully described by the specification.

For example, C-terminally and N-terminally shortened sequences are described within the specification at, for example, page 16, lines 14-25 and at page 27, line 27 to line 33 where it is stated:

> ...C- and/or N-terminally shortened, e.g. processed forms or for modified forms (e.g. by changes at proteolytic cleavage sites, glycosylation sites or

specific domain regions) or for fragments, e.g., the various domains, of the TNF receptor.

Exemplary conservative substitutions are described at Table 1 on page 17 and page at 17, line 28 to page 18, line 5.

Glycosylation of the TNF-IP and potential substitutions thereof are described, for example, at page 25, lines 6-36. Claims 67 and 68 are directed to pharmaceutical compositions comprising a polypeptide of claim 69 or 83, respectively. Such compositions are described at page 38, line 29 to page 39, line 22. In addition, the specification provides for a TNF inhibitory protein expressed in CHO cells (see Example 19, part c on page 79, line 9 to page 80, line 20).

Claims 104, 105, 107, and 108 are dependent on claim 103. Applicants maintain that these dependent claims relate to polypeptides of claim 103 comprising certain modifications such as the addition of an amino acid at the amino or carboxyl terminus of a polypeptide such as those described above.

New claims 110-114 find support at pages 78, 79, and 81 of the instant specification. Therein, transfection and expression of such a protein in COS-7 cells is described at pages 78 and 81; expression in a specific variety of CHO cells is shown on page 79.

In stark contrast to the disclosure of the instant invention, Wallach provides only partial and incomplete amino acid sequence of a partially purified protein and is completely silent as to DNA sequence information (see part a, above). The incomplete disclosure of Wallach is coupled to speculative, hypothetical schemes for determining the complete amino acid sequence of TNF-IP and DNA molecules encoding TNF-IP. And, it has further been shown by both Wallach and others that his paper examples do not provide sufficient guidance for the skilled artisan, in that those procedures could not be utilized to isolate a DNA encoding TNF-IP.

In addition, Wallach does not provide either a non-glycosylated TNF-IP or TNF-IP that has been glycosylated by CHO cells, as instantly claimed by Applicants. As Wallach provides a protein mixture prepared from human urine, the proteins contained therein have the naturally occurring glycosylation pattern found *in vivo*, assuming the isolation procedure did not affect glycosylation. Without a recombinant DNA molecule

encoding TNF-IP, Wallach could not have produced a non-glycosylated TNF-IP. In addition, in the absence of such a DNA molecule, Wallach could not have generated TNF-IP having the glycosylation pattern present following expression in CHO cells.

Applicants further provide a reference by Corti et al. (attached as **Exhibit E**) which describes differences between urine-derived soluble TNF receptor and that expressed in CHO cells. Specifically, it was found that there are differences in the composition of the N-linked sugars between urine-derived and CHO cell-expressed soluble TNF receptor. In addition, urine-derived soluble TNF receptor contains O-linked glycoslyation, while the CHO cell-expressed form does not (see page 147, col. 1, third full paragraph to page 148, col. 2).

Ex parte Aggarwal, 23 U.S.P.Q.2d 1334 (1992) relates to the possibility that glycosylation patterns may alter the activity of a claimed polypeptide, thus distinguishing it from the prior art. In that case, appellants argued that the skilled artisan would not have reasonably expected a recombinant "LT" protein to have same activity as natural LT because native glycosylation would be expected to vary. Consistent with that case, Applicants maintain that the instantly claimed polypeptide is further distinguished from Wallach because it is non-glycosylated or is glycosylated by a CHO cell.

Thus, the major differences between the instant invention and specification as compared to Wallach can be summarized as follows:

1. *Wallach* discloses only a *partial and incomplete* amino acid sequence of TNF-IP;
2. The instant specification describes the complete amino acid sequence;
3. *Wallach* does *not disclose any DNA* sequence information; and,
4. The instant specification describes the complete DNA sequence of TNF-BP.
5. In the absence of a recombinant DNA, Wallach could not have provided a recombinantly produced TNF-IP that is either non-glycosylated or glycosylated in CHO cells.

c. The third *Graham v. John Deere* factor: the level of skill in the art

Applicants' conclusions as to obviousness have been undertaken in view of the ascertainable level of skill of David Wallach, his co-inventors, and others that were active in the field at the time the Wallach application was filed. Such other persons would include those referred to in the attached Declaration by Dr. Mountz (i.e., Loetscher et al.; Schall et al.; EP 417563). As described therein, the ordinary skilled artisan was not able to follow the procedures allegedly provided by the '953 specification (Wallach) to generate the claimed polypeptides using the reagents available as of its filing date. It was only after multiple, laborious attempts by several research groups that the unpredictable DNA sequence was finally obtained and the complete amino acid sequence could be known. Thus, Wallach did not provide a specification sufficient to enable one of skill in the art to obtain the claimed DNA sequences without undue experimentation.

The inability of an expert to predict the results obtainable with a claimed product suggests non-obviousness, not routine experimentation. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988) As an example of an unpredictable art, hybridoma technology has been described as an unpredictable art where "the routineer is unable to forsee what particular antibodies will be produced" in a given experiment. *Ex parte Old*, 229 U.S.P.Q. 196 (B.P.A.I. 1985) The Federal Circuit has also addressed the unpredictability of molecular biology by stating "...because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein." *In re Bell*, 991 F.2d 781, 784 (Fed. Cir. 1993). The Federal Circuit has further held that prior knowledge of an amino acid sequence does not render the DNA encoding that protein obvious. *In re Deuel*, 51 F.3d 1555 (Fed. Cir. 1995). Thus, molecular biology is an unpredictable art in that the skilled artisan is unable to reasonably predict the DNA sequence encoding a particular protein.

d. The fourth *Graham v. John Deere* factor: objective indicia of nonobviousness

Wallach is a non-enabling reference and cannot serve as a proper reference for a 35 U.S.C. § 103(a) rejection of the instant claims. As described above, failure of others is almost irrefutable evidence of non-obviousness (Markey, C.J., *Panduit v. Dennison Manufacturing*, 774 F.2d 1082 (Fed.Cir. 1986)). Applicants argue herein that failure of

the inventor himself would provide even stronger evidence of non-obviousness. Wallach was not able utilize the teachings of his specification to isolate the either the complete amino acid sequence or a DNA sequence encoding TNF-IP at the time of filing his application. It was only with multiple attempts using reagents that were not available at the time of filing the Wallach patent that a sequence relating to TNF-IP was isolated.

(1.) Wallach is not an enabling reference as evidenced by both his own failures and those of others.

(A.) Failure of Wallach

As described in the Declaration of Dr. Mountz (**Exhibit C**), a series of patent publications and other publically-available references demonstrate several unsuccessful attempts by some or all of the inventors named in the Wallach patent to isolate a DNA molecule encoding TNF-IP according to the methods described in the Wallach patent. Wallach was eventually able to demonstrate the cloning of a full-length TNF IP cDNA (Nophar et al., 1990, **Appendix H** of the Mountz Declaration). However, this success was reached well after the effective filing date of the '953 patent and required techniques and reagents that were either not available in 1988 or were not disclosed in the '953 patent. One significant factor in Wallach's isolation of a full-length TNF-IP clone was the method used to construct the various cDNA libraries that were probed for TNF-IP hybridizing sequences. Wallach was able to obtain a partial TNF-IP cDNA clone (i.e., C2) by screening a colon cDNA library constructed from randomly-primed cDNA. Earlier efforts using liver, placenta, and HeLa cDNA libraries derived from oligo dT-primed cDNA had yielded no TNF-IP-positive clones. A full-length TNF-IP cDNA was then obtained by using a C2-derived probe to screen a CEM lymphocyte cDNA library constructed from randomly-primed and oligo dT-primed cDNA. An earlier effort using the C2-derived probe to rescreen the colon library and to screen the placenta library failed to generate a full-length TNF-IP cDNA clone.

Although Wallach was unable to obtain TNF-IP clones from oligo dT-primed cDNA libraries, the '953 patent teaches the construction of cDNA libraries "by means well known in the art" (column 12-line 5). At the time of the '953 filing, Wallach was

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clearly familiar with such means, yet his own disclosure led him to nothing more than random experimentation.

(B.) Failure of Others

In a signed Declaration, Dr. John D. Mountz, M.D., Ph.D. describes the Wallach specification and the repeated attempts by both Wallach and others to isolate the complete TNF-IP sequence using the methods described within the Wallach specification. As described above, failure of others is almost irrefutable evidence of non-obviousness (Markey, C.J., *Panduit v. Dennison Manufacturing*, 774 F.2d 1082 (Fed.Cir. 1986)). As shown herein, not only did others repeatedly fail to use the methods and reagents available as of the 1988 filing date of Wallach to determine the full length sequence of TNF-IP or to isolate a DNA encoding TNF-IP, but Wallach was not able to accomplish the task. Accordingly, Applicants submit that Wallach is a non-enabling reference.

For example, researchers at Hoffman-LaRoche reported their cloning of the TNF receptor, the extracellular domain of which is now recognized to be the source of TNF-IP (Loetscher *et al.*, 1990, *Cell* 61: 351-359; **Appendix K** of the Mountz Declaration). These researchers reported that "conventional cloning" using "relatively short, fully degenerate or longer best-guess oligonucleotides" for screening cDNA libraries was "technically difficult" and had not resulted in cloning TNF-BP (p.356). Sources of mRNA for preparing cDNA libraries for screening included human placenta and the human cell line HL60 (p. 357). These researchers successfully obtained a cDNA clone encoding the TNF receptor only after producing a 78bp cDNA fragment using the polymerase chain reaction, and screening a λgt11 library with this probe. Wallach makes no mention of using polymerase chain reaction to produce either cDNA or probes for screening cDNA.

In yet another example, researchers at Boehringer Ingleheim screened cDNA libraries prepared from placenta and human cell lines U937, Hs913T and HeLa using mixtures of degenerate oligonucleotide probes derived from the amino-terminal amino acid sequence disclosed in the '953 patent (European Patent Application EP417563; **Appendix M** of the Mountz Declaration). These experiments failed to produce a cDNA encoding TNF-IP. It was only when these researchers produced a PCR fragment using

the amino acid sequence of an internal tryptic peptide fragment that a cDNA encoding TNF-IP was obtained. Wallach does not identify any appropriate internal peptide fragment for preparing non-degenerate oligonucleotide probes. In addition, Wallach does not disclose cDNA cloning or screening methods using the polymerase chain reaction.

In another example, researchers at Genentech reported their cloning of the TNF receptor (Schal *et al.*, 1990, *Cell* 61: 361-370; **Appendix L** of the Mountz Declaration). These researchers prepared TNF-IP using a different biochemical purification protocol than that reported in the '953 patent; this protocol included affinity chromatography using immobilized TNFα (p. 361). In addition, these researchers produced two purified proteolytic fragments from this preparation that were used to prepare oligonucleotides for screening placental and HL60 cDNA libraries made in λgt10 (p. 368). The oligonucleotide primers used to screen these libraries were not degenerate, and were specifically derived from less polymorphic regions of the protein using the codon usage rules of Lathe *et al.* (p. 368). Wallach does not identify any appropriate internal peptide fragment for preparing non-degenerate oligonucleotide probes. Also, Wallach does not describe screening cDNA libraries with non-degenerate oligonucleotide probes.

Thus, Wallach himself, as well as at least the research groups at Hoffman-LaRoche, Genentech and Boehringer Ingleheim, failed to obtain a complete amino acid sequence or DNA encoding TNF-IP using the teachings of the Wallach patent. Clearly, the Wallach patent offerred the reader only an invitation to experiment. Accordingly, Applicants maintain the instant invention is not obvious in view of Wallach.

(2.) Wallach does not meet the written description requirements of the Federal Circuit for recombinant DNA claims.

Wallach issued from an application filed on April 30, 1992 that is a continuation of an application originally filed Sept. 12, 1988. Between the filing date of the Wallach application and the present, the position of both the PTO and Federal Circuit with regard to obviousness and the 35 U.S.C. § 112, first paragraph, written description requirement for recombinant DNA molecules has become increasingly clear. As shown below, unless a DNA sequence is explicitly described by way of sequence in the specification of a patent application, it cannot meet the written description requirements. Wallach does not

provide any DNA sequence information. Accordingly, Wallach cannot properly be used as a reference for supporting an obviousness rejection of the instantly-pending claims.

Wallach does not satisfy the written description requirements under 35 U.S.C. § 112, first paragraph because he does not set forth the DNA sequence encoding TNF-IP. In 1993, the Federal Circuit held that a claim to a DNA sequence must be supported by a specification setting forth the sequence of the DNA molecule. As held in *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993) (and later cited by *Regents*, below):

> [A]n adequate written description of a DNA requires more than a mere statement that it is part of the invention and a reference to a potential method for isolating it; *what is required is a description of the DNA itself.* (Emphasis added) *Fiers* at 1170.

Wallach provides only partial and incomplete amino acid sequence of one portion of TNF-IP. Wallach does not provide a description of <u>any</u> DNA, and thus fails to satisfy the written description requirement as set forth by the Court.

Applicants claimed invention cannot be obvious in view of Wallach because Wallach discloses only a partial and incomplete amino acid sequence, which is not predictive of the requisite DNA sequence. In 1993, the Court addressed the obviousness of a DNA sequence where an amino acid sequence is known. *In re Bell*, 991 F.2d 781 (Fed. Cir. 1993). It was held therein that the disclosure of the amino acid sequence of a protein does not render obvious a claim to a specific nucleic acid sequence. Specifically, the Court stated at 784:

> ...because of the degeneracy of the genetic code, there are a vast number of nucleotide sequences that might code for a specific protein...given the nearly infinite number of possibilities suggested by the prior art, and the failure of the prior art to suggest which of those possibilities is the human sequence, the claimed sequence would not have been obvious.

In the instant case, Wallach does not even provide a complete amino acid sequence for TNF-IP. The only sequence provided is partial and incomplete. And, there is a complete absence of DNA sequence information in Wallach. Thus, consistent with *Bell*, Applicants suggest that the disclosure of a partial and incomplete amino acid sequence by Wallach cannot render the instant invention obvious.

Similarly, *In re Deuel* held that a specific DNA is not obvious merely by prior art knowledge of the amino acid sequence of the protein encoded by the DNA. (51 F.3d 1555

(Fed. Cir. 1995) In that case, Deuel's application contained full, complete and non-ambiguous amino acid and cDNA sequence for heparin binding growth factor (HBGF). At issue was an obviousness rejection based on the Bohlen reference showing the first 19 amino acids of human heparin binding brain mitogen (HBBM)) in combination with a general molecular biology textbook. At 1558 of *Deuel*, it was held that the "...redundancy of the genetic code permits one to hypothesize an enormous number of DNA sequences coding for the protein." At 1599 of that case, it was further held that "...Bohlen's disclosure of the N-terminal portion of a protein, which the PTO urges is the same as HBGF, would not have suggested the particular cDNA molecules...."

Similarly, in the instant case, Wallach has disclosed only a partial N-terminal sequence and does not disclose any DNA sequence. One skilled in the art could envision an enormous number of DNA sequences coding for TNF-IP, as suggested in *Deuel* for HBBM. Wallach's disclosure does not provide any DNA sequence. Consistent with the holding in *Deuel*, in the absence of such information, Applicant's invention cannot be rendered obvious by Wallach.

Wallach has not provided a precise definition of the claimed recombinant DNA; thus, Applicants' invention cannot be rendered obvious by Wallach. The Federal Circuit revisited the written description requirement for recombinant DNA molecules in 1997. *Regents of the State of California v. Eli Lilly & Co.*, 119 F.3d. 1559 (Fed. Cir. 1997). At 1566 of that case, the Court held that an adequate written description "requires a precise definition, such as by *structure, formula, chemical name, or physical properties*" and cannot be merely a wish or plan for obtaining the claimed chemical invention. (Emphasis added) (citing *Fiers*, above). In the instant case, Wallach has not provided any definition at all for a DNA molecule encoding TNF-IP, much less a "precise definition." Wallach has provided only a partial and incomplete amino acid sequence and has provided no DNA sequence. It cannot be said, then, that Wallach has described or disclosed either the complete amino acid sequence or a recombinant DNA encoding the instantly claimed invention.

(3.) Wallach does not satisfy the written description requirements of the PTO Interim Guidelines for Examination of Patent Applications.

The Interim Guidelines for Examination of Patent Applications (Federal Register, Vol. 63, No. 114, June 15, 1998; online via *www.upsto.gov/go/notices/fr986-27.html*), suggests that the Examiner should determine: 1) what the claim as a whole covers; 2) whether there is a sufficient written disclosure to inform a skilled artisan that applicant was in possession of the claimed invention at the time the application was filed; and, 3) for each claimed genus, whether there is sufficient written description to inform the skilled artisan that applicant was in possession of the claimed genus at the time the application was filed. For example, it is to be determined whether "one skilled in the art can readily envision a sufficient number of members of the claimed genus to provide written description support for the genus...," citing *Eli Lilly*, 119 F.3d at 1568.

Here, Applicants contend that, given the limited disclosure of Wallach and the enormous potential number of species that could potentially be covered by claim 1 of Wallach, written description support simply does not exist. In addition, Applicants maintain that: 1) Wallach has not disclosed a complete structure of the recombinant DNA of claim 1; and, 2) Wallach has not disclosed <u>any</u> identifying characteristic of a recombinant DNA, with the exception that somewhere within that sequence should be a region encoding the partial and incomplete amino acid sequence illustrated therein. And, finally, Wallach has not even disclosed a single species of recombinant DNA. Therefore, Applicants do not believe he is entitled to a claim covering the multitude of potential recombinant DNA's that may contain a sequence encoding the partial and incomplete amino acid sequence disclosed by Wallach. Thus, Applicants do not believe the claims of Wallach would meet the written description requirements of the Interim Guidelines.

(4.) The instant case is distinguished from cases suggested for consideration by the Examiner.

The Examiner suggested that Applicants consider the following PTO cases with respect to the instant obviousness rejections. Applicants have done so, and distinguish each case from the instant case in turn.

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In *Ex parte Gray*, 10 USPQ2d 1922 (1989), it was stated that "...the court has often held that obviousness does not require absolute predictability." (referring to *In re Merck and Company, Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986) and *In re Lamberti*, 545 F.2d 747, 192 USPQ 278 (CPA 1976)). Applicants do not dispute that there may be occasions where absolute predictability is not required. Here, however, Wallach has not even provided a minimal amount of predictability. He has disclosed only a partial and incomplete amino acid sequence and has not provided any DNA sequence. Wallach has not described the claimed invention. As shown above, the methods provided by Wallach did not even allow Wallach himself to follow his own specification to isolate of a recombinant DNA encoding TNF-IP. Additionally, several other groups were also not able to follow his instructions to isolate the claimed invention. Thus, in the instant case, Applicants maintain that Wallach has not provided any predictability as to the nature of the claimed invention.

In *Ex Parte Movva*, 31 U.S.P.Q.2d 1207 (1993) a claim to a cDNA to swine growth hormone ("SGH") was held to be obvious in view of prior art references disclosing: 1) partial amino acid sequence of SGH; 2) homology to human ("HGH") and bovine growth hormone ("BGH"); 3) cloning of BGH cDNA using rat growth hormone ("RGH") cDNA for hybridization; 4) amino acid and nucleotide homologies between BGH, HGH, and RGH. It was held that this information would provide a reasonable expectation of success in isolating SGH cDNA via the disclosed procedure using RGH, BGH or HGH probes. Here, the Board states that the "gene of interest [SGH] is part of a family of mammalian genes, the sequences of at least three are know, and shown to share highly conserved sequences." From this, it was concluded that there was sufficient information such that the SGH cDNA could be found to be obvious.

However, in the instant case, there were no other family members described at the time of filing the Wallach application. Here, no sequence was known that corresponds to the instant invention. All that is provided by the prior art is a partial sequence from a fragment of a TNF inhibitory protein. There is no disclosure of any complete sequence, neither amino acid nor DNA. Thus, Applicants maintain that the instant case can distinguished from *Movva*.

The Board, in *Ex Parte Goldgaber*, 41 U.S.P.Q.2d 1172 (1995), held that a cDNA encoding brain beta-amyloid polypeptide would have been prima facie obvious given primary reference disclosing two sets of fully degenerate oligonucleotide probes suitable for isolating the cDNA and second reference describing techniques for constructing and screening cDNA libraries. Wallach provides not a single example or suggested oligonucleotide probe. In the *Goldgaber* case, the Board distinguished the *Bell* and *Deuel* cases in part by noting that the prior art references cited against the *Goldgaber* claims provided the skilled artisan with a complete set of degenerate oligonucleotide probes and the method for obtaining the claimed DNA with a reasonable expectation of success. The instant case is very different on its facts. Wallach provides no DNA sequence and only partial and incomplete amino acid sequence. Unlike the *Goldgaber* case, it cannot be said that Wallach could be combined with a manual related to molecular biology to isolate the claimed DNA sequence. Much more was required in this case than in the *Goldgaber* case. In fact, the methods disclosed in the '953 patent were attempted, both by Wallach and by others, and these attempts uniformly met with repeated failure. Thus, an obviousness argument, based on *Goldbager*, that Wallach renders the instant invention obvious, would fail.

2. Suggestion in the Prior Art

Wallach does not suggest nor provide any reasonable expectation of success in making the instantly claimed invention. The Federal Circuit has also reiterated the manner in which obviousness rejections are to be reviewed. Where claimed subject matter has been rejected as obvious in view of a combination of prior art references, "a proper analysis under section 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991), cited *In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit emphasized by succinctly summarizing: "Both the suggestion and the reasonable

expectation of success must be founded in the prior art, not the Applicants' disclosure." Id. Wallach provides only a partial and incomplete amino acid sequence for TNF-IP and does not provide any DNA sequence. Contrary to the Examiner's position, Wallach does not suggest doing what the applicants have done.

CONCLUSIONS AS TO OBVIOUSNESS

Applicants maintain that the instant claims cannot be found obvious in view of the Wallach reference. In summary, Wallach: 1) is a non-enabling reference; 2) fails the written description requirements; 3) has not provided a suggestion and a reasonable expectation of success in carrying out the instantly claimed invention.

First, Wallach is not an enabling reference. As shown above, Wallach provides only a partial and incomplete amino acid sequence of the TNF-IP. This sequence includes sixteen amino acid residues, wherein one of the residues is undefined ("X") and one of the residues is theoretical (Cys at the 4th position). The Examiner alleges that, given the partial amino acid sequence provided and what was known in the art at the time of filing, the instantly claimed invention is obvious in view of Wallach. Applicants have pointed out the difficulties encountered by both Wallach himself as well as several other groups of investigators in attempting to obtain the recombinant DNA claimed by Wallach. As described above, failure of others is strong evidence of a lack of obviousness. Here, Applicants have shown not only the failure of others, but failure of the inventor himself. Accordingly, Applicants maintain that Wallach cannot be said to be enabling.

Secondly, Wallach fails the written description requirement as set forth by the Courts and the PTO alike. Much of the case law surrounding the written description requirement for recombinant DNA molecules has emerged since the filing date of the Wallach application. Wallach provides only a limited disclosure of a partial amino acid sequence of TNF-IP. Wallach provides absolutely no disclosure of a DNA sequence. As held by the Federal Circuit, to satisfy the written description requirement, a claim to a recombinant DNA must provide the sequence of the DNA itself. Wallach has not provided such a sequence. Consideration of Wallach as suggested by the PTO in the Interim Guidelines can only result in the conclusion that Wallach would not convince the

skilled artisan that he had possession of the claimed invention at the time of filing. Again, Applicants have demonstrated herein the great difficulty encountered both by Wallach himself and others in actually obtaining the claimed DNA for several years after the filing of the Wallach application. Thus, it cannot be properly concluded that Wallach satisfies the written description requirements of 35 U.S.C. § 112, first paragraph. Accordingly, Applicants maintain that Wallach cannot be said to provide a description of Applicants' invention.

And, finally, Applicants maintain that Wallach does not provide either the suggestion or the reasonable expectation of success in making the instantly claimed invention. Wallach provides only a partial and incomplete amino acid sequence of a protein of undefined character. At the time of filing, the skilled artisan could only conclude that the potential DNA sequences encoding TNF-IP were vast in number, and Wallach provides only an incomplete disclosure of a partial amino acid sequence. There is no description of a DNA sequence of any kind. Thus, Wallach cannot be said to have provided the skilled artisan with a suggestion of the instant invention.

In addition, Wallach has not provided any reasonable expectation of success. Applicants have provided evidence of this by way of the Declaration of Dr. John D. Mountz and by presentation of multiple references documenting the difficulties encountered both by Wallach himself and other investigators in attempting to isolate the claimed DNA. It has been shown herein that Wallach was not able to carry out his own instructions provided in the specification to isolate the claimed invention. It has also been shown herein that others also failed in their attempts to utilized the methods provided by Wallach. Thus, the expectation of success, if any, provided by Wallach, could not be said to have been reasonable.

As such, Applicants submit that the instant invention is not obvious in view of Wallach. Accordingly, Applicants respectfully request that the obviousness rejections of claims 49-53, 67-68, and 69-106 be withdrawn.

CONCLUSION

In view of the amended claims and discussion, Applicants respectfully submit that all of the instant claims are allowable and that a Notice of Allowance should be issued in this case. The Applicants urge the Examiner to contact the Applicants' undersigned representative if the Examiner believes this would expedite prosecution of this application.

Reconsideration of the application is respectfully requested and a favorable determination is earnestly solicited.

Date: Feb 26, 1999

Respectfully submitted,

John J. McDonnell
Reg. No. 26949